Vaccine 34 (2016) 6707–6714

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine impact: Benefits for human health

Mark Doherty [a,*], Philippe Buchy [b], Baudouin Standaert [a], Carlo Giaquinto [c], David Prado- Cohrs [d]

[a] GSK Vaccines, 20 Avenue Fleming, Parc de la Noire Epine, B-1300 Wavre, Belgium
[b] GSK Vaccines, 150 Beach Road, Singapore
[c] University of Padova, Department of Woman and Child Health, Via Giustiniani 3, Padova, Italy
[d] GSK & Universidad Francisco Marroquín, School of Medicine and School of Nutrition, 23 Avenida 6-22 Zona 15, Vista Hermosa, Guatemala

ARTICLE INFO

Article history:
Available online 20 October 2016

Keywords:
Vaccine
Impact
Effectiveness
Herd protection
Cost
Health economics

ABSTRACT

Unlike most drugs, whose benefit is restricted to the individual who takes the drug, prophylactic vaccines have the potential for far-reaching effects that encompass health service utilisation, general health and wellbeing, cognitive development and, ultimately, economic productivity. The impact of immunisation is measured by evaluating effects directly on the vaccinated individual, indirectly on the unvaccinated community (herd protection), the epidemiology of the pathogen (such as changing circulating serotypes or prevention of epidemic cycles), and the additional benefits arising from improved health. Aside from protection of the individual, the broader success of immunisation is dependent on achieving a level of coverage sufficient to interrupt transmission of the pathogen. When evaluating the cost-effectiveness of vaccines, all of these potential benefits need to be accounted for. In many countries where immunisation programmes have been highly successful, the control of disease has meant that the benefits of immunisation have become less obvious. Once a well-known and much-feared disease appears to have disappeared, individuals, including healthcare professionals, no longer view ongoing prevention with the same sense of urgency. Reduced coverage is inevitably associated with resurgence in disease, with outbreaks potentially leading to significant morbidity and loss of life. Ensuring the continued success of immunisation programmes is the responsibility of all: individuals, healthcare professionals, government and industry.

1. Introduction and historical perspective

Prophylactic vaccination is one of the cheapest and most effective forms of medical intervention. From Jenner's work in 1796, to new vaccines based on our better understanding of molecular biology, immunisation has reduced the consequences of catastrophic infections. In the 18th century we had the vaccinia virus vaccine, in the 19th, Louis Pasteur and Émile Roux demonstrated that inactivated or attenuated organisms could provide protection and, in the 20th century, we experienced an accelerated development of new vaccines involving many new technologies.

"*Millions of human lives, as I shall show, have been preserved by the fruits of Jenner's genius; yet today, thousands upon thousands of men, some intelligent though designing, some intelligent though deluded, the great mass of them fanatical and ignorant, decry vaccination as not only being of no service to humanity, but positively a nuisance injurious to health and life, while millions of our fellow men are utterly ignorant of, or indifferent to the matter.*" These words written by Eugene Foster and published in 1896 [1] were relevant introductory remarks for his publication on the statistical evidence of the value of immunisation, and are still relevant today. It is astonishing how in some ways, things have not changed, despite the measurable impact of vaccines.

This paper reviews how to measure impact both from the clinical and from the health economics standpoint. A wider range of assessments of the value of immunisation, including the importance at a population level and adherence to immunisation programmes, are explored. There is a clear need for appropriate surveillance to evaluate immunisation strategies, and the means to ensure future success is discussed.

Abbreviations: GAVI, the Global Vaccine Alliance; GDP, gross domestic product; HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IQ, intelligence quotient; OPV, oral polio vaccine; QALY, quality adjusted life year; UMV, universal mass vaccination; US, United States; USD, US dollars; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: mark.x.doherty@gsk.com (M. Doherty), philippe.x.buchy@gsk.com (P. Buchy), baudouin.a.standaert@gsk.com (B. Standaert), carlo.giaquinto@unipd.it (C. Giaquinto), david.c.prado@gsk.com (D. Prado- Cohrs).

http://dx.doi.org/10.1016/j.vaccine.2016.10.025
0264-410X/

2. How is the impact of vaccines measured?

Immunisation has been controversial since its introduction, with opponents claiming it was unnatural or contaminating [2]. Despite this, immunisation has become one of the most widespread and successful of all health interventions after the provision of safe drinking water. The reason for this is simple: the first immunisation campaigns were directed at diseases that had very high mortality and morbidity in their communities. The dramatic impact of immunisation on diseases which had previously been considered an unavoidable part of everyday life was so great, and so readily visible, that public support for immunisation was overwhelming.

Subsequent programmes to finally eradicate smallpox and today, to eradicate poliomyelitis, were built on the same kind of public consensus. The benefits of eradicating a well-known and much-feared disease are so obvious, that once it becomes technically feasible, the public and political support needed to carry out the programme is assured. This can still be seen today; the 2014 Ebola epidemic in West Africa inevitably generated political pressure to develop vaccines for the disease. But beyond the obvious health benefits, it is estimated that the eradication of smallpox; which cost roughly 100 million US dollars (USD) in total, generates annual savings of 1.35 billion USD [3]. The polio eradication campaign, once completed, is likewise expected to save about 1.5 billion USD per year, and millions of lives [4]. But the polio eradication campaign also highlights one of the factors which make measuring impact so important, and so difficult; which is, that as formerly-feared diseases disappear, the benefits of immunisation become less clear-cut, while the costs remain visible (see Box 1).

Box 1 The paradox of vaccination.

The oral polio vaccine (OPV) is a live attenuated vaccine. Although cheap to use and highly effective, it has the very rare side effect of actually causing paralytic poliomyelitis in roughly 1 in a million recipients [63]. While this risk is negligible when compared to the 1 in 200 risk from natural infection, it starts to become significant once the disease has been eradicated in a region. For that reason, once natural polio infections are controlled, it makes sense to switch to the inactivated vaccine despite a resulting higher cost for the vaccine programme. But determining exactly at what point this switchover should be made requires balancing the extra resources required against the risk of disease. For this kind of decision, one can no longer rely solely on public consensus, because the risks are so small that they become invisible to the general public; including many medical practitioners, who will never see a case of paralytic polio in their entire career. By contrast, the increased costs are readily visible. Paradoxically, this effect can also apply to diseases which remain common. For example, varicella infection is a highly infectious disease that affects virtually all individuals in unvaccinated communities [64]. Although death and disability from chickenpox are rare, the extremely high number of varicella infections means that cases of encephalitis and post-varicella stroke still constitute a significant burden of disease in children [65]. At the same time, the very large number of uncomplicated infections means that chickenpox is overwhelmingly viewed as a benign infection by the general public and those medical professionals who don't deal with the severe cases. In addition, varicella infection in childhood can lead to reactivated disease later in life (zoster) which has a high risk of severe disease; but the temporal gap between varicella infection in childhood and zoster in retirement means that the visceral, obvious link between vaccination and reduction of disease, based on personal experience, is lost.

To build the case that immunisation is an effective and worthwhile intervention against infection where the most serious consequences may be long delayed after infection (human papillomavirus [HPV], hepatitis B virus [HBV], varicella, etc.) or where serious illness is rare (meningococcal infection, varicella) impact data is required. Ironically, in the developed world, where once-common infections such as tetanus, diphtheria and measles have been essentially eliminated by immunisation, impact data is also required to retain public support for continued immunisation. This is discussed in detail in the following sections.

3. Efficacy, effectiveness and impact

Vaccine efficacy corresponds to the direct protection to vaccinated individuals provided by the vaccine under optimal conditions, and usually focuses on the prevention of clinically apparent outcomes (e.g., meningitis, hospitalisation, death). When an infectious agent is able to cause a range of different clinical manifestations, the primary analysis will focus on one specific clinical manifestation (e.g., invasive pneumococcal disease during a pneumococcal vaccine study) while secondary analyses may include other clinical manifestations as endpoints (e.g., pneumonia, bronchiolitis, otitis media). For some vaccine studies, primary endpoints may not always correspond to clinically apparent disease at the time because the goal is to prevent a disease that may only appear later in life (such as cancer after HPV infection). Surrogate endpoints (e.g., immunological monitoring or isolation of the infectious agent) can then be used in order to shorten and reduce the costs of phase 3 trials. In some instances the primary analysis may look only at the prevention of the infection in relation to the microorganism types contained in the vaccine. Because of the cross-protection conferred e.g., by pneumococcal conjugated vaccines, HPV vaccines, and rotavirus vaccines, secondary analyses may include non-vaccine-type related infections. Adequate choice of primary endpoint is extremely important as it directly impacts on the selection of the most appropriate study design. However, because vaccine efficacy does not consider the background incidence of the disease, it may not reflect the full public health impact of the vaccine [5].

Vaccine effectiveness refers to the protection conferred by immunisation in a defined population. It measures both direct (vaccine-induced) and indirect (population-related) protection. The effectiveness of a vaccine is proportional to its efficacy but is also affected by vaccine coverage, access to health centres, costs and other factors not directly related to the vaccine itself.

Defining the impact of a vaccine is more complicated. International agencies like the World Health Organization (WHO), the European Medicines Agency and the Centers for Disease Control and Prevention have no consensus on what defines impact. For example one can estimate vaccine impact by comparing the incidence of a disease in the same population before and after the introduction of the vaccine or, in theory, by comparing one vaccinated and one similar unvaccinated population at the same time (see Box 2).